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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,420	04/29/2005	Hongming Chen	TPI5020USPCT1	4171

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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,420	CHEN ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/06, 04/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Preliminary amendment filed on 04/29/05, is acknowledged. Claims 7-23 are cancelled. Claims 1-6 are pending in the application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2, 4 and 6 are unclear, as to whether they claim the steps of the method, or conditions for performing the method.

In the beginning the examiner would like to notice that if the steps recited in claim 2 are a continuation of the steps recited in claim 1, it would be logical to assign sequential letters to them, rather than to start with step (a).

Step (b) should be rewritten as "analyzing the solid remaining in a sample ...".

Further, while steps (a) and (b) are active method steps, it is not apparent, as to what "steps" (c)-(k) might be, since they do not seem to recite any active method steps. Rather, it appears that they recite the characteristics of the samples.

Furthermore, it appears that the same claim recites different characteristics of the same samples, which renders the scope of the claim indefinite. Also, elements (i)-(k) recite different amounts of the same sample, which renders the scope of the claim indefinite:

> "a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd.

App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949)."

In the present instance, claims 2, 4 and 6 recite the broad recitation, "the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample", and the claims also recite specific different forms of the compounds, which is the narrower statement of the range/limitation. Also, the claims recite the broad recitation, "the amount of the compound is less than 100 μg", and the claims also recite that the amount of the compound is less than 50 μg and less than 10 μg, which is the narrower statement of the range/limitation.

For the purpose of examination the examiner considers the broadest recitation of the claim, i.e. that two samples exist in different forms, and that the amount of the compounds is less than 100 μg.

Moreover, the language of the claims the way they are written is not supported by the specification. The examiner did not find anywhere in the specification defining different forms of the compounds as the method steps. On the contrary, all embodiments for the methods disclosed in the specification comprise conventional method steps.

Claim 4 seems to contradict the parent claim 3, since it is not apparent as to how it is possible to determine how much compound-of-interest is dissolved in the liquid portion of each sample as a function of time, if the liquid portion is separated from the solid prior to determination. It is not clear, as to how it is possible to monitor the progress of dissolving, which would be a different wording for step (c), if the compound is separated from the solvent before the measurement starts. From step (c) of claim 4 it is not apparent, as to whether the sub-arrays are prepared besides the arrays of the samples prepared according to the parent claim.

Step (iv) is confusing. Which "a sample" is meant to be recited in the first sub-array, to which the solvent is added? Is this any sample? Is this a duplicate of the sample in the second sub-array?

"Steps" (d)-(l) of claim 4 have the same problems as were outlined for claim 2. The same is true for claim 6.

The examiner would like to indicate that the claims recited in the provisional application 06/423,365 are written in the correct format, unlike the claims of the instant application.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. **Claims 1-6** are rejected under 35 U.S.C. 102(e) as being anticipated by Cima et al. (US 2002/0048610 A1) or .

Cima teaches "high-throughput formation, identification, and analysis of diverse solid forms" (Title), high-throughput formation comprising dissolving drug candidates in various solvents, adding different additives and subjecting libraries under various crystallization conditions, including determining solubility of different polymorphs. Specifically, the subject matter of claims 1-6 is covered by the following paragraphs in Cima's disclosure:

> "[0002] This invention is directed to the generation and processing of data derived from large numbers of samples, the samples comprising crystalline, amorphous, and other forms of solid substances, including chemical compounds. More specifically, the invention is directed to methods and systems for rapidly producing and screening large numbers of samples to detect the presence or absence of solid-forms. **The invention is suited for discovering: (1) new solid-forms with beneficial properties and conditions for their formation, (2) conditions and/or compositions affecting the structural and/or chemical stability of solid-forms, (3) conditions and/or compositions that inhibit the formation of solid-forms; and (4) conditions and/or compositions that promote dissolution of solid-forms**".

> "[0032] In one embodiment, the invention relates to arrays comprising 2 or more samples, for example, about 24, 48, 96, to hundreds, thousands, ten thousands, to hundreds of thousands or more samples, one or more of the samples comprising solid-forms in gram, milligram, **microgram, or nanogram** quantities and practical and cost-effective methods to rapidly produce and screen such samples in parallel. *These methods provide an extremely powerful tool for the rapid and systematic analysis, optimization, selection, or discovery of conditions, compounds, or compositions that induce, inhibit, prevent, or reverse formation of solid-forms.* For example, the invention provides methods for systematic analysis, optimization, selection, or discovery of novel or otherwise beneficial solid-forms (e.g., beneficial pharmaceutical solid-forms having desired properties, such as improved bioavailability, solubility, stability, delivery, or processing and manufacturing characteristics) and conditions for formation thereof. The invention can also be used to identify those conditions where high-surface-area crystals or amorphous solids are

prepared (e.g., nanoparticles) directly by precipitation or crystallization thus obviating the step of milling.
[0033] In another embodiment, the invention is useful to discover solid forms that posses preferred **dissolution** properties. In this embodiment, arrays of solid forms of the compound-of-interest are prepared. Each element of the array is prepared from different solvent and additive combinations with differing process histories. **The solids are separated from any liquid that may be present. In this way, one has obtained an array of solid forms of the compound-of-interest. One then adds, to each sample of the array, the same dissolution medium of interest.** Thus, one would add simulated gastric fluid if the application if to optimize the dissolution of drug substance in oral dosage forms. **The dissolution medium of each array element is then sampled versus time to determine the dissolution profile of each solid form.** Optimum solid forms are ones where dissolution is rapid and/or that the resulting solution is sufficiently metastable so as to be useful. Alternatively, one may be interested in solid forms that dissolve at a specified rate. Examination of the multitude of dissolution profiles will lead to the optimum solid form."

"[0139] Sub-arrays or even individual samples within an array can be subjected to processing parameters that are different from the processing parameters to which other sub-arrays or samples, within the same array, are subjected. Processing parameters will differ between sub-arrays or samples when they are intentionally varied to induce a measurable change in the sample's properties. Thus, according to the invention, minor variations, such as those introduced by slight adjustment errors, are not considered intentionally varied."

Thus, Cima teaches the method for determining how the solubility (Claims 1, 2), dissolution (Claims 3, 4), or stability (Claims 5, 6) of polymorphs depend on the solid form by preparing an array of samples with a controlled amount of the compounds-of-interest in micrograms or nanograms quantity (which is less than 100 μg), forming a liquid portion by adding a solvent and determining how much compound-of interest is dissolved in the liquid portion depending on its form. For dissolution measurements "the dissolution medium of each array element is then sampled versus time to determine the dissolution profile of each solid form." "Examination of the multitude of dissolution profiles will lead to the optimum solid form."

Regarding stability of the various polymorphs Cima discloses the following:

"[0145] Physical properties include, but are not limited to, **physical stability**, melting point, solubility, strength, hardness, compressibility, and compactability. Physical stability refers to a compound's or composition's ability to maintain its physical form, for example maintaining particle size; maintaining crystal or amorphous form; maintaining complexed form, such as hydrates and solvates; resistance to absorption of ambient moisture; and maintaining of mechanical properties, such as compressibility and flow characteristics. Methods for measuring physical stability include spectroscopy, sieving or testing, microscopy, sedimentation, stream scanning, and light scattering. **Polymorphic changes, for example, are usually detected by differential scanning calorimetry or quantitative infrared analysis**. For a discussion of the

theory and methods of measuring physical stability see Fiese et al., in The Theory and Practice of Industrial Pharmacy, 3rd ed., Lachman L.; Lieberman, H. A.; and Kanig, J. L. Eds., Lea and Febiger, Philadelphia, 1986 pp. 193-194 and Remington 's Pharmaceutical Sciences, 18th Edition, ed. Alfonso Gennaro, Mack Publishing Co. Easton, Pa., 1995, pp. 1448-1451, both of which are incorporated herein by reference."

To the examiner's understanding Cima's disclosure covers the subject matter of the pending claims.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. *Carlson et al. (US 2003/0116497 A1)* discloses "apparatus and methods for creating and testing pre-formulations and systems for same" (Title), comprising testing various solid forms for solubility, dissolving properties and stabilities depending on the solid form.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

11/21/2008